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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/674,752

01/11/2001

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294-86

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03/08/2007

EXAMINER

HADDAD, MAHER M

ART UNIT

PAPER NUMBER

1644

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
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3 MONTHS

03/08/2007

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	09/674,752	VOORBERG ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 December 2006.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 87 and 89-100 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 87 and 89-100 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

#### DETAILED ACTION

1. Claims 87, 89-9100 are pending and under examination as they read on a polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, which polypeptide comprises the variable region of the heavy chain of a human antibody with factor VIII specificity or parts thereof which at least includes the CDR3 region and a pharmaceutical composition thereof.

2. The specification is objected to because SEQ ID NO: 34 and 43; SEQ ID NO: 36 and 46; SEQ ID NO: 51 and 55; and SEQ ID NO: 53 and 58 are duplicates of each other. Clarification/Correction is required.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

4. Claims 87 and 91-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "SEQ ID NO: 28, SEQ ID NO: 32" claimed in claim 87 represents a departure from the specification and the claims as originally filed.

Applicant's amendment filed 10/29/02 does not point to the specification for support for the newly added limitations "SEQ ID NO: 28, SEQ ID NO: 32" as claimed in claim 87. However, the specification does not provide a clear support for the claimed sequences. It noted that there are discrepancies between the WO9958680 and the subsequence submission of SEQ ID NOs: 28 and 32. The instant claims now recite limitations which were not clearly disclosed in the specification and recited in the claims as originally filed.

5. Claims 87 and 91-100 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide capable of specific binding to factor VII and interference with the activity of factor VIII inhibitors, wherein the polypeptide is scFv-EL-14, scFv-IT-2 (**once the Deposit is satisfied**) and a composition thereof, does not reasonably provide enablement for an isolated polypeptide capable of specific binding to factor VIII and comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody, wherein the heavy chain variable region

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comprises a sequence selected from the group consisting of SEQ ID NO: 23, 25, 27, 28, 32, 34, 36, 38, 51 and 53 in claims 87-90 or the pharmaceutical compositions in claims 98-100. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification under Example 2, discloses that the resulting 24 fragments were pooled according to VH-gene family and the six different fragments were digested with NcoI and Sall. Further, the vector pHEN-1-VIrep contains a light chain repertoire derived of two non-immunized donors, wherein insertion of a heavy chain repertoire in this vector has been shown to result in the production of antibody fragments that consist of the variable domains of both heavy and light chain. The antibody fragments have been termed scFv. Under Example 3, the specification selected for antibodies that binds factor VIII.

However, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979) (of record). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that fusion proteins as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of FVIII antibody have the required binding function. The specification provides no direction or guidance regarding how to produce any light chain variable region of the claimed antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

Regarding the pharmaceutical compositions of claims 98-100, it has been established that in the absence of a correlation between the in vitro and in vivo efficacy the person having ordinary skill in the art has no basis for perceiving these efficacy. "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals" (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

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Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

The declaration by Dr. Voorberg under 37 CFR 1.132 filed 1/25/07 is insufficient to overcome the rejections because the specification only show that scFv- EL-14 and scFv-IT-2 can neutralize the activity of factor VIII inhibitors using Bethesda assay wherein scFv contain both the heavy and light chains. The Gilles' et al antibodies are not analog to the claimed human antibody in the instant invention. Further, Gilles's et al antibodies are directed against another antibodies (anti-idiotypic antibodies) while the instant antibodies are directed to FVIII.

6. Claims 87 and 91-100 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of an isolated polypeptide capable of specific binding to factor VIII and comprising a heavy chain variable region of a human antibody with factor VIII specificity and a light chain variable region of a human antibody, wherein the heavy chain variable region comprises a sequence selected from the group consisting of SEQ ID NO: 23, 25, 27, 28, 32, 34, 36, 38, 51 and 53 in claims 87 89-90 or the pharmaceutical compositions in claims 98-100.

Applicant has disclosed only the scFv-EL14 and scFv-IT2 antibodies; therefore, the skilled artisan cannot envision all the contemplated light chain sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3<sup>rd</sup> column).

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Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 5, 2007



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